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By Lauren Martz, Staff Writer

Researchers at the **Dana-Farber Cancer Institute** and the **Baylor College of Medicine** have shown that **Tensha Therapeutics Inc.**'s bromodomain inhibitors could prevent sperm production and be developed as a male contraceptive.<sup>1</sup> The biotech, which is focused on developing the molecules for cancer, has exclusive rights to the findings and is interested in pursuing bromodomain inhibitors in the indication.

Available options for male contraception are limited to barrier methods and vasectomy. There are no male contraceptive drugs on the market. Several hormone-based strategies are in the clinic but carry the risk of systemic side effects.

Indeed, Michael O'Rand, professor of cell biology and developmental biology at **The University of North Carolina at Chapel Hill**, said not all men react the same way to testosterone-based contraceptives and that testosterone can cause increased aggression. Nor can the therapies be delivered orally because they are quickly destroyed in the body.

These issues suggest nonhormonal strategies could be more successful. The first clues that bromodomain inhibitors could be good candidates emerged in 2007 when a group at **Columbia University Medical Center** found that genetic knockout of bromodomain testis-specific (BRDT), a bromodomain-containing protein specifically found in the testis, caused sterility in male mice.<sup>2</sup>

Bromodomains are protein domains that bind to acetylated lysines and are involved in chromatin remodeling.

Additional evidence that BRDT could be a male contraceptive target came in 2010 when a group at **The University of Utah School of Medicine** showed that mutations in *BRDT* were associated with male infertility in a genomewide association study.<sup>3</sup>

Now, groups from Dana-Farber and Baylor have teamed up to determine how bromodomain inhibitors affect male fertility. The researchers found JQ1, a bromodomain inhibitor that acts against proteins including BRDT and bromodomain containing 4 (BRD4), had a hormone-independent contraceptive effect in male mice.

The groups were led by James Bradner, assistant professor in the Department of Medicine at **Harvard Medical School** and investigator and staff physician in the Department of Medical Oncology at Dana-Farber, and Martin Matzuk, professor of developmental biology at Baylor College of Medicine.

The paper also included researchers from the **University of Oxford**, **Texas A&M University**, **Boston Children's Hospital** and **The George Washington University School of Medicine and Health Sciences**.

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Pharmacologic and crystallography studies showed that JQ1 bound and competitively inhibited BRDT. In mice, intraperitoneal (i.p.) dosing resulted in significant concentrations of the compound in testicular tissue, suggesting the molecule is capable of crossing the blood-testis barrier and could be a good contraceptive candidate.

In mice, i.p. injection of JQ1 decreased testicular volume, seminiferous tube volume, number of spermatids, sperm count and sperm motility compared with vehicle injection. JQ1 did not affect serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) or testosterone, suggesting that any contraceptive activity was caused by a hormone-independent effect on the reproductive germ cells.

The team then tested the effect of the BRDT inhibitor on fertility and mating behavior in mice. Injection of 100 mg/kg/day of JQ1 completely prevented male mice from siring offspring when mated with females for one month. Lower doses reduced litter numbers and size, suggesting a dose-dependent contraceptive effect.

Finally, the team found that within one to three months of discontinuing JQ1, physiological effects of the drug including reduced testicular volume, sperm count and sperm motility were reversed. Fertility also was restored in the mice. Compared with vehicle-treated controls, mice previously treated with JQ1 sired similar size and number of litters and produced offspring of normal size, behavior and activity.

Results were published in *Cell*.

**Getting testes specific**

Bradner told SciBX that the next steps for pursuing the contraceptive indication include developing an inhibitor that is specific for BRDT.

Christina Wang, professor of medicine in the Division of Endocrinology & Metabolism at the **Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center**, said special attention will

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need to be paid to the off-target effects of bromodomain inhibitors, which affect gene expression.

O’Rand said the team will need to prove that the compound does not affect mitosis elsewhere. In particular, he said activity on lymphocytes during an immune response should be analyzed because JQ1 originally was studied for its effect in cancers including myeloid leukemia.

Matzuk and Bradner believe that the design of BRDT-specific inhibitors should reduce the risks of these types of off-target effects. “Because JQ1 binds to some BRDT-related proteins, our goal is to develop a drug that blocks only BRDT and would theoretically have less side effects,” Matzuk said.

“Prior genetic and our chemical genetic studies suggest that selective BRDT inhibition will confer

profound effects on spermatogenesis and fertility without significant symptoms, in particular without affecting the male sex hormone axis,” said Bradner.

Wang said high regulatory standards and the proven safety and efficacy of female contraceptives may result in limited interest by pharmaceutical companies in BRDT inhibitors for male contraception.

O’Rand agreed that the FDA likely will set a higher bar for bromodomain inhibitors in contraception than it would in cancer but thinks the market is worth tackling.

“Female contraceptives are a huge industry estimated to be worth about \$17 billion by 2015, and depending on how you collect the data, there are really good signs that male contraceptives could be accepted by a lot of people and that the market is really there,” he said. “A lot of women are unable or unwilling to take the birth control pill for various reasons, so a real target is men in committed relationships with these women. Through surveys, we are also finding that men of certain demographics seem particularly responsive to the idea of taking a contraceptive pill.”

Matzuk agreed that there is room for both male and female contraceptives. “The pill for women has the drawback that it alters hormone levels,” he said.

Tensha CEO Doug Onsi said the company is interested in the potential of bromodomain inhibitors as male contraceptives but declined to provide a timeline for the program.

**“Prior genetic and our chemical genetic studies suggest that selective BRDT inhibition will confer profound effects on spermatogenesis and fertility without significant symptoms, in particular without affecting the male sex hormone axis.”**

—James Bradner,  
Harvard Medical School

### Other angles

Blocking spermatogenesis with strategies such as BRDT inhibition is not the only option for male contraception. For example, O’Rand said his team is developing a molecule that inhibits sperm motility to prevent fertilization of the egg.

He said, “A potential issue with a contraceptive that is shutting off the supply of sperm is that it will not be immediately effective. A patient would need to wait a long time, maybe more than 60 days, before the contraceptive activity kicks in. Like with a vasectomy, it might also be necessary to use some type of test with this contraceptive strategy to determine whether sperm production has stopped and when the treatment will be effective.”

Wang agreed. She said blocking spermatogenesis may have slower activity by blocking sperm at the source than contraceptives that affect sperm after they have been produced.

Tensha’s Onsi told *SciBX* that Dana-Farber filed patent applications covering the composition of matter for JQ1 and other bromodomain inhibitors. He said that Dana-Farber and Baylor jointly filed separate IP relating to use of the compounds in male contraception. Tensha has exclusive rights to both sets of IP.

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# Passenger mutations take the wheel

By Tim Fulmer, Senior Writer

Two research groups have independently shown that targeting genes carrying passenger mutations blocked growth of cancer cells and improved survival in mouse models.<sup>1,2</sup> Although precise therapeutic windows for such a strategy remain to be determined, the researchers are already planning to develop therapeutics that exploit the presence of those mutations to inhibit tumor growth.

Hotly pursued cancer targets are usually proteins encoded by tumor suppressor genes and oncogenes such as *BRAF* and *BCR-ABL tyrosine kinase* because mutations in those genes promote malignant transformation and drive disease progression. However, most solid tumors also accumulate thousands of mutations in other genes over the course of disease.

Those passenger mutations may not promote tumor development like driver mutations but can nonetheless disrupt genes in metabolic and housekeeping pathways that are necessary for long-term tumor survival.<sup>3-6</sup> Thus, targeting the proteins encoded by those mutated genes could offer a way to slow tumor growth or at least sensitize tumor cells to cancer therapies that hit other pathways.

The challenge is identifying candidate genes susceptible to such passenger mutations in tumors. Two academic groups approached the problem using detailed genetic analyses of the solid tumor genome.

A team led by Ronald DePinho, president of **The University of**

**Texas MD Anderson Cancer Center**, primarily focused on passenger mutations that occur in housekeeping genes that are near a particular tumor suppressor region in the tumor genome. The other study, led by William Hahn and Rameen Beroukhim, professors of medicine at the **Dana-Farber Cancer Institute**, focused on passenger mutations that occur in housekeeping genes across many regions of the tumor genome. Hahn is also associate professor of medicine and Beroukhim is also assistant professor of medicine at **Harvard Medical School**.

DePinho and colleagues initially noted that many metabolic and housekeeping genes occur as redundant homologs to ensure cells remain viable if one gene homolog is deleted or disrupted. They hypothesized that if a passenger mutation removed or inactivated one homolog of a housekeeping gene, the tumor cells would become highly sensitive to inhibition of the only remaining homolog.

To find such redundant housekeeping genes, the researchers looked at The Cancer Genome Atlas data set for glioblastoma to find deletions in genes involved in essential cell activities.<sup>7</sup>

One of their top hits was a gene encoding the essential glycolytic enzyme enolase 1 $\alpha$  (*ENO1*), which is located next to a tumor suppressor locus that is deleted in 1%–5% of glioblastomas. That suggested the *ENO1* gene might also be susceptible to deletion or inactivation. Indeed, expression profiling showed that 5 of 359 glioblastoma samples and 2 glioblastoma cell lines lacked expression of *ENO1* when the tumor suppressor locus also was missing.

As expected, those cell lines were highly sensitive to inhibition of enolase 2 $\gamma$  neuronal (*ENO2*), the remaining enolase homolog in neuronal cells. In two glioblastoma cell lines lacking *ENO1*, small hairpin RNA against *ENO2* inhibited cell growth.

In the same cell lines, the small molecule enolase inhibitor

**Table 1. Potentially targetable passenger mutations in cancer.** Two papers, one published in *Nature* and the other in *Cell*, identified mutations that occur in genes involved in the cellular housekeeping and metabolic functions of tumor cells. Below are the top hits.

Muller <i>et al.</i>		
Gene abbreviation	Encoded protein	Cellular pathway
<i>ENO1</i>	Enolase 1 $\alpha$	Glycolysis and gluconeogenesis
<i>H6PD</i>	Hexose-6-phosphate dehydrogenase	Pentose phosphate shunt
<i>KIF1B</i>	Kinesin family member 1B	Chromosomal segregation
<i>NMNAT1</i>	Nicotinamide nucleotide adenyltransferase 1	Nicotinamide dinucleotide (NAD) biosynthesis
<i>UBE4B</i>	Ubiquitination factor E4B	Ubiquitin-dependent degradation
<i>ACO1 (IRP1)</i>	Aconitase 1	Iron metabolism and citric acid cycle
<i>KLHL9</i>	Kelch-like 9	Chromosomal segregation
<i>PANK1</i>	Pantothenate kinase 1	Acetyl-CoA biosynthesis
<i>KIF20B</i>	Kinesin family member 20B	Chromosomal segregation
Nijhawan <i>et al.</i>		
Gene abbreviation	Encoded protein	Cellular pathway
<i>PSMC2</i>	Proteasome 26S subunit ATPase 2	Proteasome-mediated degradation
<i>EIF2B2</i>	Eukaryotic translation initiation factor 2B subunit 2 $\beta$	Protein synthesis
<i>EEF2</i>	Eukaryotic translation elongation factor 2	Protein synthesis
<i>PHF5A</i>	PHD finger protein 5A	Spliceosome-mediated mRNA splicing
<i>HPGD (15-PGHD)</i>	Hydroxyprostaglandin dehydrogenase 15 NAD	Prostaglandin metabolism
<i>RPS15</i>	Ribosomal protein S15	Component of 40S ribosome subunit
<i>SNRPB</i>	Small nuclear ribonucleoprotein polypeptides B and B1	Pre-mRNA splicing
<i>POLR2F</i>	Polymerase RNA II DNA-directed polypeptide F	Component of RNA polymerase
<i>USPL1</i>	Ubiquitin-specific peptidase-like 1	Ubiquitin-dependent degradation

phonoacetoxyhydroxamate (PHAH) lowered growth compared with vehicle. In wild-type glioblastoma cells expressing both *ENO1* and *ENO2*, the inhibitor failed to reduce growth.

The final result confirmed that a passenger deletion in one homolog was sufficient to make tumor cells susceptible to loss or inhibition of the remaining homolog.

The findings, which were published in *Nature*, are part of a research program that began at Dana-Farber and then continued at MD Anderson when DePinho was appointed president of the center last year.

In the second paper, Hahn, Rameen and colleagues set out with the similar hypothesis that loss of tumor suppressor genes might involve loss of other nearby genes involved in the stress response, which could reduce the fitness of tumor cells.

To test that idea, the researchers undertook a systematic investigation of the copy number status of more than 7,000 genes in 86 different cancer cell lines.<sup>8</sup> The group narrowed the list to 56 candidate genes for which expression of only a single copy increased susceptibility to cell death compared with expression of both copies of the gene.

Many of the candidate genes encoded proteins that were subunits of protein complexes essential to cellular survival, including the spliceosome, proteasome and the ribosome. The top hit was the gene encoding proteasome 26S subunit ATPase 2 (*PSMC2*), which is part of the regulatory complex of the 26S proteasome.

To test the therapeutic potential of suppressing *PSMC2* *in vivo*, the researchers used tumor-specific nanoparticles to deliver anti-*PSMC2* small interfering RNA to mouse ovarian xenografts. In xenografts expressing only a single copy of *PSMC2*, the siRNA decreased tumor burden by more than 75% and increased survival compared with control siRNA.

However, in xenografts expressing normal levels of *PSMC2*, the siRNA failed to reduce tumor burden or improve survival, confirming that a passenger deletion in one copy of *PSMC2* made ovarian cancer cells more susceptible to inhibition of the second copy.

The results were published in *Cell*.

Passenger mutations “may be the Achilles heel of cancer genomes” and “should create many opportunities for personalized medicine,” wrote Ben Lehner and Solip Park in a commentary accompanying the *Nature* paper.<sup>9</sup> Lehner and Park are researchers in the Centre for Genomic Regulation at **Pompeu Fabra University**.

### From mutations to molecules

Both groups now plan to develop inhibitors of the proteins identified in the papers. The teams also will look for passenger mutations in other proteins and tumor types.

The enolase inhibitor used in the *Nature* paper “needs further exploration in terms of off-target pharmacology, pharmacokinetics and safety profile before it could be considered for clinical development,” lead author Florian Muller told *SciBX*.

He noted that enolase is a relatively unexplored target, and as a result the team is “performing high throughput screens to look for alternative chemical scaffolds that may be better starting points” for drug development.

Based on the findings in the *Cell* paper, Hahn said the Dana-Farber group plans to identify ways to inhibit specific proteasome subunits such as *PSMC2*. He said the researchers also want to expand their approach

to other tumor types to identify additional candidate genes but declined to provide additional details.

DePinho, Muller and colleagues will continue to look at glioblastoma. “There are many more *ENO1/ENO2*-type pairs in the glioblastoma cancer genome, and we would like to experimentally validate other examples as we did in the *Nature* paper for *ENO1*,” said Muller, who is an instructor at MD Anderson.

Other researchers on the DePinho team include Simona Colla, an instructor at MD Anderson, and Elisa Aquilanti, a medical student at the **Albert Einstein College of Medicine of Yeshiva University**.

### Targeting the housekeeper

The two papers provide a rationale for tumor-selective targeting of metabolic and housekeeping genes, which have generally not been considered promising targets in oncology (see Table 1, “Potentially targetable passenger mutations in cancer”).

Housekeeping genes have been avoided as drug targets “because of the rational assumption by the drug discovery community that it would be difficult to develop a therapeutic window when inhibiting a protein that every cell in the body needs,” said Erica Golemis.

She said the *Nature* paper now points out that “this limitation does not necessarily apply and hence opens up a much broader class of protein targets for therapeutic development. It might be useful to develop specific catalytic inhibitors of housekeeping genes, then partner with informatics/genomics providers to establish in which tumors those inhibitors might be particularly valuable,” she said.

Golemis, deputy CSO and VP of the **Fox Chase Cancer Center**, is using RNAi screens to identify proteins that influence the sensitivity of cancer cells to epidermal growth factor receptor (EGFR)-based therapies.<sup>10</sup>

Marion Dorsch, VP of biology at **Agios Pharmaceuticals Inc.**, said the two papers “underscore the need for sophisticated genetics and metabolomics capabilities to identify the right intervention points in these pathways where cancer cells are unable to compensate but normal cells can.”

Agios mines genomic data and conducts large-scale metabolomics experiments in tumor tissues to identify sensitive metabolic nodes in tumors that are vulnerable to inhibition. The company’s lead program is in preclinical development and focuses on the cancer metabolism target isocitrate dehydrogenase 1 (IDH1).

Agios also has a discovery-stage program focused on another cancer metabolism target, pyruvate kinase M2 isozyme (PKM2). In 2009, Agios researchers published in *Nature* that mutations in IDH1 lead to excess levels of the cancer-associated metabolite 2-hydroxyglutarate.<sup>11</sup>

### Narrow window

The genome-based approaches used in the two papers could have limitations, including a narrow therapeutic window and the potential to engender treatment resistance.

**“It might be useful to develop specific catalytic inhibitors of housekeeping genes, then partner with informatics/genomics providers to establish in which tumors those inhibitors might be particularly valuable.”**

**—Erica Golemis,  
Fox Chase Cancer Center**

“First, this approach requires expensive, detailed genotyping of many malignancies to find the few for which each specialized gene-specific agent might be applicable,” said Paul Bingham, VP of research at **Cornerstone Pharmaceuticals Inc.** “Second, it remains to be seen how many common tumors will offer frequently deleted redundant and/or essential genes. Finally, given that metabolism is complex in its pathway branching, the approach could be susceptible to developing resistance.”

Cornerstone’s strategy is to attack tumor-specific regulatory processes that are general and not confined to tumors that have gene-specific alterations. The approach ensures that “we get broad potential tumor coverage and off-target adverse effects on noncancer cells are mitigated if not eliminated,” said Bingham.

Cornerstone’s lead compound is CPI-613, a lipoate analog that targets the metabolic enzyme pyruvate dehydrogenase. The compound is in Phase I/II testing to treat advanced hematological malignancies. In mouse xenograft models of non-small cell lung cancer (NSCLC) and pancreatic cancer, CPI-613 decreased tumor volume and increased survival compared with vehicle.<sup>12</sup>

Ultimately, the major challenge for targeting housekeeping genes in cancer “is to demonstrate a therapeutic window and examine toxicity,” said Jason Moffat. “We know these housekeeping genes are essential for the proliferation of most cell types, so identifying the cohort of patients that demonstrate sensitivity to a possible drug is going to be key moving forward.” Moffat is assistant professor of molecular genetics at the **University of Toronto**.

Moffat said his lab is developing profiles of essential genes for multiple cancer cell lines and then combining that information with genomic information to develop a genetic interaction atlas of cancer cells.

The findings in both papers are covered by patents and available for licensing.

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## COMPANIES AND INSTITUTIONS MENTIONED

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# Putting a cap on AD

By Lev Osherovich, Senior Writer

In the wake of recent Phase III failures of antibodies against  $\beta$ -amyloid to treat Alzheimer's disease, **AC Immune S.A.** and **Swiss Federal Institute of Technology Lausanne** researchers have unveiled an alternative—a class of small molecules that directly block amyloid fibril growth.<sup>1</sup> If the compounds can be made to enter the brain, the approach could arrest the growth of amyloid plaques upstream of the usual target points for antibodies.

Amyloid fibrils are repetitively structured polymers of  $\beta$ -amyloid ( $A\beta$ ), a protein fragment produced in the brains of patients with AD, and are thought to trigger inflammatory activity and neuronal death. Fibrils grow by trapping monomers of  $A\beta$  at their ends, eventually forming the large amyloid plaques that are the hallmark of AD histopathology.

Numerous therapeutics have aimed to either block production or aggregation of  $A\beta$  and thus prevent the growth of fibrils. Previously, academic researchers had screened for small molecule modulators of  $A\beta$  polymerization, but those screens yielded only nonselective compounds like metal chelators and fibril-binding dyes.<sup>2</sup>

The AC Immune team had sought an alternative to these nonspecific amyloid-binding compounds and used insights into the structure of  $A\beta$  fibrils to rationally design a class of molecules that cap off the ends of fibrils.

“These are rationally designed nondye compounds that are optimized for  $\beta$ -sheet-containing aggregates,” said CTO and R&D head Andreas Muhs, who led the team. “These compounds bind to the ends of fibrillar structures and prevent growth.”

Muhs' team used an *in vitro* assay to screen a family of 3-aminopyrazole compounds for the ability to bind to fibril ends and arrest their growth.

The best hits were dimeric 3-aminopyrazoles with aromatic substituents. Muhs suspected that this type of compound fits tightly into the  $\beta$ -sheet pocket at the ends of each fibril and blocks the recruitment of further monomers.

Consistent with this prediction, electron microscopy of fibrils grown *in vitro* in the presence of the top hits of the series revealed stunted and amorphous aggregates, whereas fibrils grown in the presence of vehicle were highly regular.

The best of the compounds also prevented *in vitro* growth of smaller, oligomeric aggregates of  $A\beta$  that some researchers think are the true causal agents in AD. Indeed, oligomers cause acute neurotoxicity in cell culture models of AD, but the relevance of oligomers in clinical AD remains controversial.<sup>3</sup>

The best compounds from the AC Immune team lowered the extent of oligomer-mediated cell killing compared with vehicle, thus suggesting the compounds can act on both fibrils and oligomers.

Results were published in *The Journal of Biological Chemistry*.

## Avoid the amyloid

The AC Immune team's findings suggest a model in which capping the ends of oligomers or fibrils prevents amyloid growth and subsequent toxicity (see **Figure 1**, “Blocking amyloid growth”). Muhs said the company is developing an unnamed member of the 3-aminopyrazole family as a lead compound in a preclinical small molecule program in AD.

Although the compounds work well *in vitro*, how putting a cap on amyloid fibrils would affect AD pathology *in vivo* remains unclear.

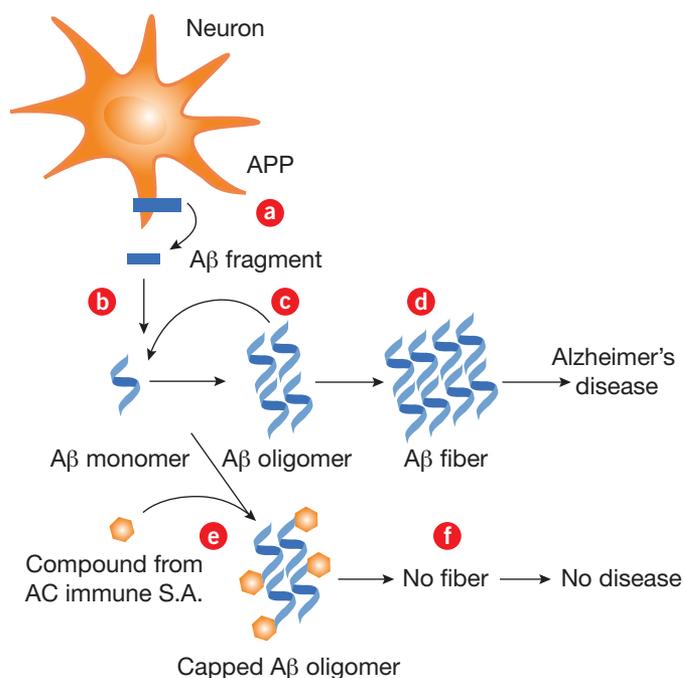
Jonathan Weissman, professor of biochemistry and cellular and molecular pharmacology at the **University of California, San Francisco**, said he was “pretty skeptical that capping approaches represent a viable therapeutic option. It's not clear that amyloids are the toxic agent, and even if you did cap them they would probably break and generate new ends.”

Muhs acknowledged that the breakdown of amyloid fibrils into smaller fragments could be a concern.

“You don't want to cut the fibril in the middle and make more ends,” he said. “You have to make sure that you don't break the fibrils into something smaller that is more toxic.”

Another concern is whether the amyloid-capping compounds can readily penetrate the brain, as the molecules tended to be hydrophobic and thus would be excluded by the blood brain barrier.

AC Immune's most advanced AD therapeutic is the amyloid-binding mAb crenezumab (MABT5102). The compound is partnered with **Roche's Genentech Inc.** unit and is in Phase II testing to prevent progression of an aggressive hereditary form of AD. In June, AC



**Figure 1. Blocking amyloid growth.** Kroth *et al.* have designed small molecules to block the formation and growth of amyloid, an aberrant protein thought to cause Alzheimer's disease (AD).

In AD, amyloid precursor protein (APP) is proteolytically cleaved to produce the  $\beta$ -amyloid ( $A\beta$ ) fragment [a]. This fragment is thought to spontaneously fold into an aberrant structural form [b] prone to clumping together in other misfolded molecules of its type [c]. Over time, this oligomeric aggregate grows into a large, structurally repetitive amyloid fibril [d].

**AC Immune S.A.**'s small molecules bind to the ends of amyloid oligomers and fibrils, blocking their growth [e] and thus preventing AD progression [f].

Immune partnered with Genentech to develop antibodies against another AD target, microtubule-associated protein- $\tau$  (MAPT; TAU; FTDP-17).

**“These are rationally designed nondye compounds that are optimized for  $\beta$ -sheet-containing aggregates. These compounds bind to the ends of fibrillar structures and prevent growth.”**

—*Andreas Muhs,*  
*AC Immune S.A.*

“The compounds we have described here are quite specific for A $\beta$ , but there are other molecules that have amyloid-like structures, such as  $\alpha$ -synuclein,” said Muhs. “We could use our knowledge of amyloid

Muhs said the rational design approach to amyloid-end capping eventually could be applied to other neurodegenerative diseases such as Parkinson’s disease (PD). In PD, the intracellular protein  $\alpha$ -synuclein (SNCA) forms amyloid deposits within Lewy bodies, which are among the cellular characteristics of the disease.

structure to design other compounds” that block the growth of other types of amyloids.

AC Immune has filed for patents covering the compounds used in the study, and the IP is available for licensing or partnering.

Osherovich, L. *SciBX* 5(35); doi:10.1038/scibx.2012.916  
Published online Sept. 6, 2012

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# Peptide scaffolds for VEGF delivery

By Kai-Jye Lou, Staff Writer

The clinical development of VEGF-based strategies to treat ischemic cardiovascular diseases, first proposed over 10 years ago, has been challenging due to the difficulty of maintaining local VEGF concentrations at therapeutic levels.<sup>1,2</sup> Researchers at the **National Cheng Kung University** in Taiwan have developed a potential solution to the problem—an injectable self-assembling peptide nanofiber scaffold that enables sustained VEGF delivery and establishes a microenvironment that augments arteriogenesis and cardiac repair following myocardial infarction.<sup>3</sup> The group is evaluating the scaffold in porcine studies and hopes to submit an IND in two to three years.

Patrick Hsieh, an associate professor at the Institute of Clinical Medicine at the National Cheng Kung University (NCKU), said clinical trials of VEGF-based strategies to treat cardiovascular diseases have primarily relied on infusion of the protein itself or gene delivery and have not shown convincing evidence of therapeutic efficacy.

“So far, these strategies for VEGF delivery have not been very successful,” he told *SciBX*. “And researchers in this field now realize that one cannot simply inject VEGF into the heart as it will be quickly washed out.”

Moreover, newly formed blood vessels will regress within two weeks after VEGF delivery if they are not supported and maintained through maturity.<sup>4,5</sup> A final reason to improve control over VEGF delivery and confine it to the heart is that the factor itself causes vascular leakage, which can lead to systemic side effects such as hypotension, proteinuria and edema.

Data from the largest Phase II trial of recombinant human VEGF—the investigator-led VIVA (Vascular endothelial growth factor in Ischemia for Vascular Angiogenesis) trial—showed that intracoronary and i.v. infusions of the molecule offered no improvement over placebo.<sup>6</sup> Companies such as Vascular Genetics Inc. (now part of **Madrigal Pharmaceuticals Inc.**) and **GenVec Inc.** have previously advanced VEGF-based gene therapies for cardiovascular diseases as far as Phase II trials before dropping their programs.

Hsieh hypothesized that an effective delivery system for the factor needs to check three boxes: create a microenvironment that is conducive to the recruitment and engraftment of new cells in the ischemic region, establish a VEGF concentration gradient that attracts cells to the region and provide a localized, constant supply of the factor to support newly formed vasculature until it becomes mature blood vessels.

To address these challenges, Hsieh turned to an injectable self-assembling peptide nanofiber scaffold he began developing as a postdoctoral scholar at **Harvard Medical School**. In 2005 and 2006, Hsieh and his colleagues at Harvard reported that this self-assembling peptide scaffold could facilitate the sustained delivery of other growth factors to the heart, such as platelet derived growth factor (PDGF) and insulin-like growth factor-1 (IGF-1).<sup>7,8</sup>

The Harvard group also showed that the scaffold itself could create a microenvironment favorable to endothelial cells, which make up the inner lining of blood vessels.<sup>9</sup>

In the current study, the NCKU group combined a recombinant human VEGF isoform with a self-assembling peptide nanofiber scaffold. Over a period of 28 days, intramyocardial injection of the VEGF-containing scaffold in rat and porcine models of myocardial infarction (MI) improved cardiac function and increased both angiogenesis and arteriogenesis compared with injection of scaffold or VEGF alone.

In the rat model, intramyocardial injection of the VEGF-containing nanofiber scaffold decreased systemic adverse effects compared with injection of VEGF alone. Hsieh said the team did not see systemic or local side effects in the pig model either. Studies to evaluate the long-term effects of the VEGF-containing scaffold as well as the scaffold itself are underway.

Surprisingly, the researchers found that in addition to promoting the recruitment of cells involved in the generation of new vasculature, the VEGF-containing scaffold also promoted the recruitment of cardiomyocyte precursors. This suggests the scaffold could have the added benefit of helping generate new cardiac muscle in addition to new vasculature.

Although the experiments only evaluated effects over one month, Hsieh noted that the peptide scaffold itself degrades slowly and persists for up to four months at the injection site.

Results were published in *Science Translational Medicine*.

“Our scaffold maintains a consistent VEGF concentration gradient, which is important for guiding reparative endogenous cells to the injection site,” said Hsieh. “Our scaffold also allows the VEGF to be retained in the heart for at least two to three weeks.”

Karen Christman, a cofounder of **Ventrix Inc.** and an assistant professor of bioengineering at the **University of California, San Diego**, noted that the mechanisms underlying the therapeutic effects of engineered scaffolds for cardiac repair have remained unclear and that the current study helps to tease out such mechanisms.

“Most investigators evaluating engineered scaffolds only assess the scaffold’s performance at a study’s endpoint, which makes it difficult to know what is going on between the time a scaffold is implanted up until that endpoint,” Christman told *SciBX*. “In this study, the researchers tracked multiple cell types that are coming into the scaffold at multiple time points and related their observations to an improvement of cardiac function.”

**“The researchers tracked multiple cell types that are coming into the scaffold at multiple time points and related their observations to an improvement of cardiac function.”**

**—Karen Christman,  
University of California, San Diego**

Ventrix is developing VentriGel, an injectable hydrogel scaffold sourced from decellularized porcine cardiac connective tissues, to prevent left ventricular remodeling and reduce heart failure following MI. Christman said the company hopes to move VentriGel into a Phase I trial next year.

## Basket of benefits

Christman said one of the clear advantages of Hsieh’s scaffold is that it is comprised of synthetic materials.

“This property gives the researchers much more control over product

consistency, which will be an advantage when scaling up production of their scaffold,” she told *SciBX*.

Michael Davis, an assistant professor of biomedical engineering and medicine at the **Georgia Institute of Technology** and **Emory University School of Medicine**, said another benefit is that the scaffold’s peptides should be easy to modify if the researchers want to adjust the properties of their scaffold.

Hsieh added that many other engineered scaffolds that have been considered for use in cardiovascular disease either degrade too fast or not at all.

Scaffolds that degrade too quickly will not allow sufficient time for new blood vessels to mature, whereas long-lived, nonbiodegradable scaffolds can trigger an inflammatory response and have other long-term side effects, he told *SciBX*.

Hsieh thinks the scaffold being developed by his group will be able to support the generation of mature vascular networks and then get degraded and cleared from the body shortly thereafter.

He added that the scaffold provides the damaged myocardium with immediate structural support following injection, which could help prevent further ventricular remodeling and deterioration of cardiac function while reparative processes get underway.

Finally, Hsieh noted that the peptide fibers of the scaffold have diameters of 10–20 nm, which falls within the range of native extracellular matrix. He said this is an important property as it creates a microenvironment that is amenable to 3D cell culture.

According to Hsieh, most other biomaterials being used in engineered scaffolds for the heart form fibers in the micrometer range, which are only amenable for 2D cell culture. This could make it difficult to recapitulate the features of native tissues.

### Timing and delivery

Hsieh said the group is running additional studies in pigs to evaluate the long-term effects of the VEGF-containing peptide scaffold.

He expects the studies to run three to six months but noted that the group might need to take the experiments out to one or two years if the FDA requires it.

In parallel, the NCKU group also is running studies to determine

the therapeutic time window for delivery of the scaffold in the post-MI setting. Hsieh thinks the scaffold probably will need to be injected shortly after an acute MI event, which is when endogenous reparative processes in the heart are most active.

Davis added that it will be important to use labeled peptides to study how the scaffold degrades and where the degradation products go, and to determine whether the scaffold and any of its degradation products have significant toxicity.

Both Davis and Christman also want to know whether the scaffold could be delivered via a less-invasive route such as a catheter.

“Doctors may be hesitant to stick a needle into the heart of an acute MI patient if they’ve already stabilized that patient,” Davis told *SciBX*.

NCKU has a pending patent covering the use of the peptide nanofiber scaffold for the delivery of VEGF. The technology is available for licensing.

Lou, K.-J. *SciBX* 5(35); doi:10.1038/scibx.2012.917

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e-mail: [phsieh@mail.ncku.edu.tw](mailto:phsieh@mail.ncku.edu.tw)
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**Georgia Institute of Technology**, Atlanta, Ga.  
**GenVec Inc.** (NASDAQ:GNVC), Gaithersburg, Md.  
**Madrigal Pharmaceuticals Inc.**, Fort Washington, Pa.  
**National Cheng Kung University**, Tainan, Taiwan  
**Harvard Medical School**, Boston, Mass.  
**University of California, San Diego**, La Jolla, Calif.  
**Ventrix Inc.**, San Diego, Calif.

## This week in therapeutics

**THE DISTILLERY** brings you this week's most essential scientific findings in therapeutics, distilled by *SciBX* editors from a weekly review of more than 400 papers in 41 of the highest-impact journals in the fields of biotechnology, the life sciences and chemistry. The Distillery goes beyond the abstracts to explain the commercial relevance of featured research, including licensing status and companies working in the field, where applicable.

This week in therapeutics includes important research findings on targets and compounds, grouped first by disease class and then alphabetically by indication.

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Autoimmune disease</b>				
Rheumatoid arthritis (RA)	CD79b molecule immunoglobulin-associated- $\beta$ (CD79B; B29)	<p>Mouse studies suggest B29 could induce anti-inflammatory T<sub>reg</sub> cells to help treat RA. In a mouse model of RA, intranasal administration of B29 blocked disease progression in both prophylactic and therapeutic settings. In the same mouse model, adoptive transfer of T<sub>reg</sub> cells from B29-immunized mice suppressed disease progression, whereas transfer of T<sub>reg</sub> cells from control peptide-immunized mice did not. Next steps include determining whether the peptide also induces human T<sub>reg</sub> cells.</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.918</b> Published online Sept. 6, 2012</p>	Patent applications filed; licensed to Trajectum Pharma B.V.	<p>van Herwijnen, M.J.C. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Aug. 13, 2012; doi:10.1073/pnas.1206803109 <b>Contact:</b> Willem van Eden, Utrecht University, Utrecht, the Netherlands e-mail: <a href="mailto:w.vaneden@uu.nl">w.vaneden@uu.nl</a></p>
<b>Cancer</b>				
Bladder cancer	Tuberous sclerosis complex tumor suppressor 1 (TSC1); TSC2; mammalian target of rapamycin (mTOR; FRAP; RAFT1)	<p>Genome sequencing suggests mTOR inhibitors may be most effective in patients with bladder cancer carrying <i>TSC1</i> mutations. In patients with bladder cancer enrolled in an ongoing Phase II trial of Afinitor everolimus, sequencing identified an association between <i>TSC1</i> mutations in primary tumors and treatment response. Patients harboring the <i>TSC1</i> mutations remained on everolimus longer and had a longer time to tumor recurrence than patients carrying wild-type <i>TSC1</i>. Ongoing work includes developing an assay to test for <i>TSC1</i> and <i>TSC2</i> mutations in all patients with cancer considered for enrollment in Phase I trials of cancer therapies at Memorial Sloan-Kettering Cancer Center.</p> <p>Afinitor, an oral mTOR inhibitor from Novartis AG, is marketed to treat brain cancer, breast cancer and neuroendocrine tumors. The drug also is in Phase III testing or earlier to treat other types of cancer.</p> <p>Torisel temsirolimus, an i.v. mTOR inhibitor from Pfizer Inc., is marketed to treat renal cancer and mantle cell lymphoma (MCL).</p> <p>Taltorvic ridaforolimus, a small molecule mTOR inhibitor from Ariad Pharmaceuticals Inc. and Merck &amp; Co. Inc., received a complete response in June for treatment of sarcoma. The compound is in Phase II testing or earlier to treat other types of cancer.</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.919</b> Published online Sept. 6, 2012</p>	Unpatented; available for licensing or partnering	<p>Iyer, G. <i>et al. Science</i>; published online Aug. 23, 2012; doi:10.1126/science.1226344 <b>Contact:</b> Barry S. Taylor, University of California, San Francisco, Calif. e-mail: <a href="mailto:barry.taylor@ucsf.edu">barry.taylor@ucsf.edu</a> <b>Contact:</b> David B. Solit, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: <a href="mailto:solitd@mskcc.org">solitd@mskcc.org</a></p>
Brain cancer	Enolase 1 $\alpha$ (ENO1); enolase 2 $\gamma$ neuronal (ENO2)	<p>Cell culture studies suggest inhibiting ENO2 in tumor cells could help treat glioblastoma. In ENO1-deficient glioblastoma cells, small hairpin RNA against <i>ENO2</i> decreased cell growth compared with scrambled shRNA. In the same cells, the pan-enolase inhibitor phonoacetohydroxamate (PHAH) lowered cell growth compared with no treatment. Next steps include optimizing the pharmacological properties of PHAH (<i>see Passenger mutations take the wheel, page 4</i>).</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.920</b> Published online Sept. 6, 2012</p>	Patented; available for licensing	<p>Muller, F.L. <i>et al. Nature</i>; published online Aug. 15, 2012; doi:10.1038/nature11331 <b>Contact:</b> Ronald A. DePinho, University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: <a href="mailto:rdepinho@mdanderson.org">rdepinho@mdanderson.org</a></p>

## This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Phosphofructokinase muscle (PFKM; PFK1)	<p>Patient sample and mouse studies suggest inhibiting glycosylation of PFK1 could help treat cancer. In samples from patients with breast and lung cancer, PFK1 glycosylation levels were two- to fourfold higher than those in adjacent normal tissues. In mice, injection of human non-small cell lung cancer (NSCLC) cells expressing a glycosylation-deficient S529A mutant <i>PFK1</i> led to formation of smaller tumors than injection of NSCLC cells expressing wild-type <i>PFK1</i>. Next steps include developing and evaluating small molecules that mimic the effects of inhibiting PFK1 activation.</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.921</b> Published online Sept. 6, 2012</p>	Provisional patent application filed; available for licensing from the California Institute of Technology Office of Technology Transfer	<p>Yi, W. <i>et al. Science</i>; published online Aug. 24, 2012; doi:10.1126/science.1222278 <b>Contact:</b> Linda C. Hsieh-Wilson, California Institute of Technology, Pasadena, Calif. e-mail: <a href="mailto:lhwh@caltech.edu">lhwh@caltech.edu</a></p>
Cancer	Proteasome 26S subunit ATPase 2 (PSMC2)	<p>Mouse studies suggest inhibiting PSMC2 in tumor cells could help treat cancer. In mouse xenograft models of ovarian cancer, tumor-targeted delivery of anti-<i>PSMC2</i> small interfering RNA decreased tumor growth and significantly increased survival compared with delivery of control siRNA (<math>p &lt; 0.0001</math>). Next steps could include screening for small molecules that selectively inhibit PSMC2. (<i>see Passenger mutations take the wheel, page 4</i>)</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.922</b> Published online Sept. 6, 2012</p>	Patented; available for licensing	<p>Nijhawan, D. <i>et al. Cell</i>; published online Aug. 17, 2012; doi:10.1016/j.cell.2012.07.023 <b>Contact:</b> William C. Hahn, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:william_hahn@dfci.harvard.edu">william_hahn@dfci.harvard.edu</a> <b>Contact:</b> Rameen Beroukhim, same affiliation as above e-mail: <a href="mailto:rameen_beroukhim@dfci.harvard.edu">rameen_beroukhim@dfci.harvard.edu</a></p>
Cancer; melanoma	Hepatocyte growth factor/scatter factor (HGF/SF); VEGF	<p>Cell culture and mouse studies suggest HGF/SF and VEGF variants that do not bind heparan sulfate (HS) could help treat cancer. Isoforms of HGF/SF and VEGF that normally bind HS as part of receptor signaling complexes were engineered to disrupt HS binding. In cellular assays, the protein variants antagonized downstream receptor signaling. In a mouse model of melanoma metastasis, intraperitoneal injection of the HGF/SF variant decreased metastatic burden compared with no injection. Next steps include evaluating the HGF/SF variant in preclinical models of other cancers and developing a recombinant expression system for the VEGF variant.</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.923</b> Published online Sept. 6, 2012</p>	Patent application filed; available for licensing	<p>Cecchi, F. <i>et al. Cancer Cell</i>; published online Aug. 14, 2012; doi:10.1016/j.ccr.2012.06.029 <b>Contact:</b> Donald P. Bottaro, National Cancer Institute, Bethesda, Md. e-mail: <a href="mailto:dbottaro@helix.nih.gov">dbottaro@helix.nih.gov</a></p>
Melanoma	Endothelin B receptor	<p>Mouse studies suggest antagonizing endothelin B receptor could help prevent or treat melanoma metastases to the CNS. In clinical samples of CNS melanoma metastases, 11 of 17 had high endothelin B receptor expression. In a mouse model of spontaneous melanoma CNS metastasis, an endothelin B receptor inhibitor plus a drug to increase blood brain barrier permeability decreased intracranial tumor size compared with the permeability-enhancing drug alone. Next steps include investigating additional targets that could play a role in melanoma CNS metastasis.</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.924</b> Published online Sept. 6, 2012</p>	Unpatented; licensing status not applicable	<p>Cruz-Munoz, W. <i>et al. Cancer Res.</i>; published online Aug. 3, 2012; doi:10.1158/0008-5472.CAN-12-2194 <b>Contact:</b> Robert S. Kerbel, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada e-mail: <a href="mailto:robert.kerbel@sri.utoronto.ca">robert.kerbel@sri.utoronto.ca</a></p>
Ovarian cancer	Inhibitor of differentiation 4 (ID4)	<p><i>In vitro</i> and mouse studies suggest inhibiting ID4 could help treat ovarian cancers. In ovarian cancer cell lines, <i>ID4</i>-targeting small interfering RNA inhibited cell proliferation compared with control siRNA. In mouse xenograft models of ovarian cancer, targeted, cancer cell-penetrating nanocomplexes loaded with <i>ID4</i>-targeting siRNA decreased tumor growth by up to 87% compared with control siRNA-loaded nanocomplexes. Next steps include studying the toxicity of the nanocomplex in additional small animal models.</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.925</b> Published online Sept. 6, 2012</p>	Patent application filed; available for licensing	<p>Ren, Y. <i>et al. Sci. Transl. Med.</i>; published online Aug. 15, 2012; doi:10.1126/scitranslmed.3003778 <b>Contact:</b> William C. Hahn, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:william_hahn@dfci.harvard.edu">william_hahn@dfci.harvard.edu</a> <b>Contact:</b> Sangeeta N. Bhatia, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: <a href="mailto:sbhatia@mit.edu">sbhatia@mit.edu</a></p>

## This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Thyroid cancer	Signal transducer and activator of transcription 3 (STAT3)	<i>In vitro</i> and mouse studies suggest inhibiting STAT3 phosphorylation could worsen thyroid cancers. In primary papillary thyroid carcinoma samples, decreased expression of tyrosine phosphorylated STAT3 (pY-STAT3) correlated with larger tumors and distant metastases. In mice transplanted with pY-STAT3-expressing thyroid cancer cells, STAT3-targeting small hairpin RNA increased tumor growth compared with scrambled shRNA. Next steps include determining the correlation between activated STAT3 levels and therapeutic outcomes in cancer. At least four companies have STAT3 inhibitors in clinical and preclinical development to treat cancers.  <b>SciBX 5(35); doi:10.1038/scibx.2012.926</b> Published online Sept. 6, 2012	Findings unpatented; unlicensed	Couto, J.P. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 13, 2012; doi:10.1073/pnas.1201232109 <b>Contact:</b> Jacqueline F. Bromberg, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: <a href="mailto:bromberj@mskcc.org">bromberj@mskcc.org</a> <b>Contact:</b> David Lyden, Weill Cornell Medical College, New York, N.Y. e-mail: <a href="mailto:dcl2001@med.cornell.edu">dcl2001@med.cornell.edu</a>

## Endocrine/metabolic disease

Contraception	Bromodomain testis-specific (BRDT); bromodomain and extra terminal domain (BET)	Mouse studies suggest targeting BRDT with BET inhibitors could be useful as a male contraceptive. In male mice, daily injections with JQ1, a small molecule BET inhibitor, caused potent inhibition of BRDT, leading to decreased testicular volume, sperm counts and sperm motility compared with daily injections of vehicle. In mouse mating studies, males receiving JQ1 sired fewer offspring than vehicle-treated controls. Next steps include developing BRDT-selective JQ1 derivatives to avoid any potential adverse effects from inhibiting other bromodomain proteins targeted by JQ1 ( <i>see New home for bromodomains, page 1</i> ).  <b>SciBX 5(35); doi:10.1038/scibx.2012.927</b> Published online Sept. 6, 2012	Patent applications filed covering inhibitor; exclusively licensed to Tensha Therapeutics Inc.	Matzuk, M.M. <i>et al. Cell</i> ; published online Aug. 17, 2012; doi:10.1016/j.cell.2012.06.045 <b>Contact:</b> James E. Bradner, Dana-Farber Cancer Institute, Boston, Mass. e-mail: <a href="mailto:james_bradner@dfci.harvard.edu">james_bradner@dfci.harvard.edu</a> <b>Contact:</b> Martin M. Matzuk, Baylor College of Medicine, Houston, Texas e-mail: <a href="mailto:mmatzuk@bcm.edu">mmatzuk@bcm.edu</a>
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## Infectious disease

Malaria	Unknown	Mouse studies identified an artemisinin-derived thioacetal thiocarbonate that could be combined with mefloquine hydrochloride to help treat malaria. In <i>Plasmodium berghei</i> -infected mice, the thiocarbonate plus mefloquine led to a mean survival of 29.8 days compared with 16.5 days for the trioxane antimalarial drug artemether plus mefloquine. Next steps could include evaluating the artemisinin-derived thiocarbonate in models of <i>P. falciparum</i> infection. Coartem artemether/lumefantrine, a fixed-dose, artemisinin-based combination from Novartis AG, is marketed to treat malaria.  <b>SciBX 5(35); doi:10.1038/scibx.2012.928</b> Published online Sept. 6, 2012	Patent and licensing status unavailable	Jacobine, A.M. <i>et al. J. Med. Chem.</i> ; published online Aug. 14, 2012; doi:10.1021/jm3009986 <b>Contact:</b> Gary H. Posner, The Johns Hopkins University, Baltimore, Md. e-mail: <a href="mailto:gph@jhu.edu">gph@jhu.edu</a>
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## Inflammation

Inflammation	Phosphoinositide 3-kinase- $\beta$ (PI3K $\beta$ ); PI3K $\delta$	Rat studies identified a pyrrolo pyridine analog as a dual inhibitor of PI3K $\beta$ and PI3K $\delta$ that could help treat inflammation. In a rat model of collagen-induced arthritis, the dual inhibitor decreased hind-paw inflammation and cartilage erosion compared with vehicle. Next steps were undisclosed but could include evaluating the lead dual inhibitor in additional animal models of inflammation. AMG 319, a small molecule inhibitor of PI3K $\delta$ from Amgen Inc., is in Phase I testing to treat hematological malignancies. GS 1101, a small molecule inhibitor of PI3K $\delta$ from Gilead Sciences Inc., is in Phase III testing to treat chronic lymphocytic leukemia (CLL) and Phase II testing to treat non-Hodgkin's lymphoma (NHL). At least six other companies have inhibitors of PI3K $\delta$ in Phase II testing or earlier to treat cancer, autoimmune diseases or inflammatory conditions.  <b>SciBX 5(35); doi:10.1038/scibx.2012.929</b> Published online Sept. 6, 2012	Patent application filed; licensing status undisclosed	Gonzalez-Lopez de Turiso, F. <i>et al. J. Med. Chem.</i> ; published online Aug. 9, 2012; doi:10.1021/jm300679u <b>Contact:</b> Felix Gonzalez-Lopez de Turiso, Amgen Inc., South San Francisco, Calif. e-mail: <a href="mailto:felgonza@amgen.com">felgonza@amgen.com</a>
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## This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Musculoskeletal disease</b>				
Osteoporosis	Follicle stimulating hormone (FSH)	<p>Mouse studies suggest antagonizing FSH could help treat osteoporosis. In a mouse model of ovariectomy-induced bone loss, a polyclonal anti-FSH antibody decreased bone resorption and increased bone formation compared with a control antibody. Ongoing work includes developing anti-FSH mAbs for additional preclinical studies.</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.930</b> Published online Sept. 6, 2012</p>	Patent application filed; licensing status unavailable	<p>Zhu, L.-L. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Aug. 20, 2012; doi:10.1073/pnas.1212806109 <b>Contact:</b> Mone Zaidi, Mount Sinai School of Medicine, New York, N.Y. e-mail: <a href="mailto:mone.zaidi@mountsinai.org">mone.zaidi@mountsinai.org</a> <b>Contact:</b> Maria I. New, same affiliation as above e-mail: <a href="mailto:maria.new@mssm.edu">maria.new@mssm.edu</a></p>
Osteoporosis	VEGF	<p>Mouse studies suggest increasing VEGF expression in bone marrow stem cells could help treat or prevent osteoporosis. Mice with conditional <i>Vegf</i> knockout in osteoblast lineage cells showed characteristics of osteoporosis, including lower bone mass and greater bone marrow fat than wild-type mice. Next steps include additional mechanistic studies.</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.931</b> Published online Sept. 6, 2012</p>	Findings unpatented; licensing status not applicable	<p>Liu, Y. <i>et al. J. Clin. Invest.</i>; published online Aug. 13, 2012; doi:10.1172/JCI61209 <b>Contact:</b> Bjorn R. Olsen, Harvard School of Dental Medicine, Boston, Mass. e-mail: <a href="mailto:bjorn_olsen@hms.harvard.edu">bjorn_olsen@hms.harvard.edu</a></p>
<b>Neurology</b>				
Alzheimer's disease (AD)	$\beta$ -Amyloid (A $\beta$ )	<p>SAR studies identified A<math>\beta</math>-binding small molecules that could help treat AD. <i>In vitro</i>, a series of 3-aminopyrazole compounds that bind the ends of A<math>\beta</math> inhibited amyloid fibril growth. In a human neuronal cell line, members of the series decreased A<math>\beta</math>-induced toxicity compared with vehicle. Next steps include conducting preclinical toxicology studies and optimizing the lead 3-aminopyrazole for brain penetration (<i>see Putting a cap on AD, page 7</i>).</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.932</b> Published online Sept. 6, 2012</p>	Patent pending; available for licensing	<p>Kroth, H. <i>et al. J. Biol. Chem.</i>; published online Aug. 13, 2012; doi:10.1074/jbc.M112.357665 <b>Contact:</b> Andreas Muhs, AC Immune S.A., Lausanne, Switzerland e-mail: <a href="mailto:andreas.muhs@acimmune.com">andreas.muhs@acimmune.com</a></p>
Alzheimer's disease (AD)	Ryanodine receptor 1 (RyR1)	<p><i>In vitro</i> and mouse studies suggest inhibiting RyR1 could help treat AD. In neuroblastoma cell lines and mouse primary neurons overexpressing mutant amyloid precursor protein (APP), Dantrium IV dantrolene inhibited RyR1 and restored calcium concentrations and decreased APP processing compared with vehicle. In a transgenic mouse model of AD, dantrolene treatment beginning after onset of AD pathology decreased learning and memory deficits and <math>\beta</math>-amyloid (A<math>\beta</math>) plaque density compared with vehicle. Next steps include developing a dantrolene-like compound with higher specificity for RyR1.</p> <p>SpePharm Holding B.V. markets dantrolene to treat hypothermia. Armgo Pharma Inc.'s RyR1 modulator, Rycals, is in Phase II testing to treat arrhythmia and heart failure.</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.933</b> Published online Sept. 6, 2012</p>	Findings unpatented; unavailable for licensing	<p>Oulès, B. <i>et al. J. Neurosci.</i>; published online Aug. 22, 2012; doi:10.1523/JNEUROSCI.0875-12.2012 <b>Contact:</b> Mounia Chami, UMR7275 Centre National de la Recherche Scientifique (CNRS) and University of Nice Sophia Antipolis, Valbonne, France e-mail: <a href="mailto:mchami@ipmc.cnrs.fr">mchami@ipmc.cnrs.fr</a> <b>Contact:</b> Frédéric Checler, same affiliation as above e-mail: <a href="mailto:checler@ipmc.cnrs.fr">checler@ipmc.cnrs.fr</a></p>
Alzheimer's disease (AD)	Unknown	<p>Mouse studies suggest the antiepileptic drug levetiracetam could help treat AD. In a transgenic mouse model of AD, levetiracetam decreased learning and memory deficits and aberrant neurological activity compared with saline. Next steps could include clinical studies.</p> <p>Keppra levetiracetam is marketed by UCB Group and GlaxoSmithKline plc for epilepsy.</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.934</b> Published online Sept. 6, 2012</p>	Patent and licensing status unavailable	<p>Sanchez, P.E. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Aug. 6, 2012; doi:10.1073/pnas.1121081109 <b>Contact:</b> Lennart Mucke, University of California, San Francisco, Calif. e-mail: <a href="mailto:lmucke@gladstone.ucsf.edu">lmucke@gladstone.ucsf.edu</a></p>

## This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Alzheimer's disease (AD); Parkinson's disease (PD)	Proteasome	<p>Mouse studies suggest inhibiting proteasome activity could help treat neurodegenerative diseases. In a mouse model of neurodegeneration, a proteasome inhibitor delayed neurodegeneration and extended survival. Compared with vehicle, the proteasome inhibitor increased assembly of the soluble, N-ethylmaleimide-sensitive fusion protein-attachment protein receptor (SNARE) complex, which is required for normal neuronal function. Next steps include testing additional drugs in animal models.</p> <p>At least five companies have proteasome inhibitors in stages ranging from preclinical to marketed to treat various cancers.</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.935</b> Published online Sept. 6, 2012</p>	Findings unpatented; available for licensing	<p>Sharma, M. <i>et al. Sci. Transl. Med.</i>; published online Aug. 15, 2012; doi:10.1126/scitranslmed.3004028 <b>Contact:</b> Manu Sharma, Stanford University, Stanford, Calif. e-mail: <a href="mailto:sharmal1@stanford.edu">sharmal1@stanford.edu</a> <b>Contact:</b> Thomas C. Südhof, same affiliation as above e-mail: <a href="mailto:tcs1@stanford.edu">tcs1@stanford.edu</a></p>
Neurology	Cardiolipin	<p>Rat and cell culture studies suggest inhibiting cardiolipin oxidation in mitochondria could help treat traumatic brain injury (TBI). In a rat model of cortical impact injury, pharmacological inhibition of cardiolipin oxidation in mitochondria postinjury increased recovery of motor and cognitive function compared with vehicle treatment. In the same rat model, inhibition of cardiolipin oxidation decreased lesion volume and neuronal cell death. Next steps include discovering and optimizing mitochondria-targeted compounds that inhibit cardiolipin oxidation.</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.936</b> Published online Sept. 6, 2012</p>	Patent applications filed; available for licensing from the University of Pittsburgh Office of Technology Management	<p>Ji, J. <i>et al. Nat. Neurosci.</i>; published online Aug. 26, 2012; doi:10.1038/nn.3195 <b>Contact:</b> Hülya Bayır, University of Pittsburgh, Pittsburgh, Pa. e-mail: <a href="mailto:bayihx@ccm.upmc.edu">bayihx@ccm.upmc.edu</a></p>
Parkinson's disease (PD)	Myocyte enhancer factor 2D (MEF2D)	<p>Mouse studies suggest activating the transcription factor MEF2D with the dimeric acetylcholinesterase (AChE) inhibitor <i>bis</i>(3)-cognitin (B3C) could help treat PD. In a mouse model of PD, B3C activated MEF2D, prevented loss of protective tyrosine hydroxylase signaling in dopaminergic neurons and rescued PD-associated movement abnormalities. Next steps include further developing the small molecule and testing it in other animal models of neurodegeneration.</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.937</b> Published online Sept. 6, 2012</p>	Patent application filed; available for licensing	<p>Yao, L. <i>et al. J. Biol. Chem.</i>; published online Aug. 13, 2012; doi:10.1074/jbc.M112.367540 <b>Contact:</b> Zixu Mao, Emory University School of Medicine, Atlanta, Ga. e-mail: <a href="mailto:zmao@pharm.emory.edu">zmao@pharm.emory.edu</a></p>
<b>Ophthalmic disease</b>				
Age-related macular degeneration (AMD)	MAP kinase 1 (MAPK1; ERK-2); MAPK3 (ERK-1); MAP kinase kinase 1 (MAP2K1; MEK1)	<p>Mouse studies suggest blocking ERK-1 and ERK-2 signaling in the retina could help treat dry AMD. In mice with Alu RNA-induced degeneration of retinal pigment epithelium (RPE) cells, intravitreal delivery of PD98059, a reagent that inhibits MEK1 and blocks phosphorylation of ERK-1 and ERK-2, decreased Alu RNA-mediated cytotoxicity compared with delivery of vehicle. Next steps could include studying additional inhibitors of ERK-1 and ERK-2 in the mice.</p> <p><b>SciBX 5(35); doi:10.1038/scibx.2012.938</b> Published online Sept. 6, 2012</p>	Patent and licensing status undisclosed	<p>Dridi, S. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Aug. 6, 2012; doi:10.1073/pnas.1206494109 <b>Contact:</b> Jayakrishna Ambati, University of Kentucky, Lexington, Ky. e-mail: <a href="mailto:jamba2@email.uky.edu">jamba2@email.uky.edu</a></p>

## This week in techniques

**THE DISTILLERY** brings you this week's most essential scientific findings in techniques, distilled by *SciBX* editors from a weekly review of more than 400 papers in 41 of the highest-impact journals in the fields of biotechnology, the life sciences and chemistry. The Distillery goes beyond the abstracts to explain the commercial relevance of featured research, including licensing status and companies working in the field, where applicable.

This week in techniques includes findings about research tools, disease models and manufacturing processes that have the potential to enable or improve all stages of drug discovery and development.

Approach	Summary	Licensing status	Publication and contact information
<b>Assays &amp; screens</b>			
Fluorescent reporter-expressing dengue virus	Fluorescent reporter-expressing dengue virus could be useful for screening and evaluating therapeutic candidates to treat the disease. A serotype-2 dengue virus was engineered to express GFP or firefly luciferase. In mice, fluorescence imaging showed that the engineered reporter virus primarily localized to lymphoid and gut tissues. An expression screening system using human hepatoma cells infected with the engineered virus showed that 12 interferon (IFN)-stimulated genes from a library of over 350 such genes inhibited viral replication. Next steps could include using the fluorescent reporter virus in studies to evaluate compounds that modulate IFN-stimulated genes.	Patent and licensing status unavailable	Schoggins, J.W. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 20, 2012; doi:10.1073/pnas.1212379109 <b>Contact:</b> Charles M. Rice, The Rockefeller University, New York, N.Y. e-mail: <a href="mailto:ricec@rockefeller.edu">ricec@rockefeller.edu</a>
<b>SciBX 5(35); doi:10.1038/scibx.2012.939</b> Published online Sept. 6, 2012			
<b>Disease models</b>			
T cell migration across the blood brain barrier (BBB)	The mechanism of T cell migration across the BBB could help identify new therapeutic targets for multiple sclerosis (MS) and other CNS-related autoimmune diseases. In a rat model of experimental autoimmune encephalitis (EAE), cell tracing studies showed that reactive T cells were unable to efficiently cross the BBB unless they first migrated to the lung, where their gene expression profiles were reprogrammed. The reprogramming downregulated expression of genes related to T cell activation and upregulated expression of genes related to cellular locomotion, adhesion and chemokine signaling. Next steps include determining whether T cells in patients with MS show a similar migratory pattern and identifying new therapeutic targets based on the changes in gene expression from reprogramming.	Unpatented; licensing status not applicable	Odoardi, F. <i>et al. Nature</i> ; published online Aug. 22, 2012; doi:10.1038/nature11337 <b>Contact:</b> Alexander Flügel, Hertie Foundation and University Medical Center Goettingen, Goettingen, Germany e-mail: <a href="mailto:fluegel@med.uni-goettingen.de">fluegel@med.uni-goettingen.de</a>
<b>SciBX 5(35); doi:10.1038/scibx.2012.940</b> Published online Sept. 6, 2012			
<b>Drug delivery</b>			
Polyethyleneimine (PEI) as an adjuvant for intranasal vaccines	PEI could boost the efficacy of intranasal vaccines against viral infections. In mice intranasally immunized with an HIV gp140-based vaccine, coimmunization with PEI induced higher gp140-specific systemic and mucosal IgG levels than mucosal adjuvants $\alpha$ -galactosylceramide, cholera toxin B or cholera holotoxin. Mice immunized intranasally with PEI and vaccines against influenza A virus or herpes simplex virus (HSV)-2 had greater protection against challenge with live influenza A virus or HSV-2 than mice immunized with vaccine and $\alpha$ -galactosylceramide or cholera toxin-based adjuvants. Planned work includes testing PEI as an adjuvant to undisclosed bacterial vaccines in animal models.	Unpatented; available for partnering	Wegmann, F. <i>et al. Nat. Biotechnol.</i> ; published online Aug. 26, 2012; doi:10.1038/nbt.2344 <b>Contact:</b> Quentin J. Sattentau, University of Oxford, Oxford, U.K. e-mail: <a href="mailto:quentin.sattentau@path.ox.ac.uk">quentin.sattentau@path.ox.ac.uk</a>
<b>SciBX 5(35); doi:10.1038/scibx.2012.941</b> Published online Sept. 6, 2012			
<b>Drug platforms</b>			
Influenza vaccine to induce broadly neutralizing antibodies	Mouse and ferret studies suggest vaccines that induce broadly neutralizing antibodies may be useful for preventing influenza virus infection, even in humans with previous influenza exposure. Past human studies have suggested induction of broadly neutralizing antibodies could be difficult in subjects with prior exposure to influenza. In mice and ferrets with pre-existing immunity to an H1N1 influenza A virus hemagglutinin (HA), a prime and boost vaccination protocol against a second H1N1 HA induced broadly neutralizing antibodies that protected the animals from challenge with two other unmatched H1N1 strains. Next steps include using the prime-boost vaccine strategy with an adjuvant in animal models of influenza challenge.	Patent application filed; certain aspects available for licensing	Wei, C.-J. <i>et al. Sci. Transl. Med.</i> ; published online Aug. 15, 2012; doi:10.1126/scitranslmed.3004273 <b>Contact:</b> Gary J. Nabel, National Institutes of Health, Bethesda, Md. e-mail: <a href="mailto:gjlabel@nih.gov">gjlabel@nih.gov</a>
<b>SciBX 5(35); doi:10.1038/scibx.2012.942</b> Published online Sept. 6, 2012			

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